Chronic Diseases - International

Open Access

Austin Publishing Group

Research Article

Smoking, Diabetes Control and Gastrointestinal Complaints

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Received: November 20, 2023
Accepted: December 30, 2023
Published: January 06, 2024

Abstract

Objecive: There is clear evidence that gastrointestinal complaints are common in patients with diabetes mellitus, especially in those who are current smokers.

Aim of the study: We aimed to analyze the frequencies of the Gastrointestinal Complaints (GIC) and the relationship between smoking, GIC, and glycemic control by glycated hemoglobin (Hb1Ac%) and Fasting Plasma Glucose (FPG) in diabetic outpatient patients.

Methods: 189 patients took part in the cross-sectional study. The questionnaire corresponding to Eexocrine Pancreatic Insufficiency (EPI) was completed at the doctor's visit. The discriminating factors were smoking, and glycemic control based on the last documented FPG and HbA1c%.

Results: The most prevalent gastrointestinal complaints in all study patients were abdominal bloating, weakness on a daily basis, and diarrhea. There was a significant relationship between short-term glycemic control assessed by FPG and some GIC patients with frequent overall presence of GIC had worse glycemic control by FPG. Increased defecation frequency, daily weakness, soft consistency tools, steatorrhea, and pancreatic enzyme replacement therapy, all were related with higher FPG values. There was a relationship between long-term glycemic control assessed by HbA1C% and some gastrointestinal complaints. HbA1c% values were higher in those diabetic patients with frequent overall presence of gastrointestinal complaints, higher defecation frequency, more frequent abdominal bloating, weakness on a daily basis, steatorrhea, and pancreatic enzyme replacement therapy usage.

Conclusions: gastrointestinal complaints are common in all outpatient patients, but are significantly more frequent in diabetic outpatient patients, especially with poor diabetes control, who have also been more likely to use pancreatic enzyme replacement therapy. The relationship between smoking, GIC, glycemic control by glycated hemoglobin (Hb1Ac%) and FPG in diabetic outpatient patients was not confirmed.

Keywords: Diabetes; Smoking; Diabetes control; Gastrointestinal complaints; Fasting plasma glycemia; Glycated hemoglobin; Exocrine pancreatic insufficiency; Outpatient

Abbreviations: DM: Diabetes Mellitus; DOP: Diabetic Outpatient Patients; EPI: Exocrine Pancreatic Insufficiency; FPG: Fasting Plasma Glucose; GI: Gastrointestinal; GIC: Gastrointestinal Complaints; HbA1c%: Glycated Hemoglobin; PERT: Pancreatic Enzyme Replacement Therapy

Citation: Peceliuniene J,Buoziene J, Zukauskaite I, Stapulionyte A, Tautaviciute G, Norkus A, Rudinskiene E. Smoking, Diabetes Control and Gastrointestinal Complaints. Chronic Dis Int. 2024; 6(1): 1032.

Introduction

There is clear evidence that Gastrointestinal (GI) Complaints (GIC) is common in patients with Diabetes Mellitus (DM) [1-4]. Many different mechanisms of action lead to the dysfunction of the enteric nervous system, such as microangiopathy, autonomic neuropathy, myopathy, polyneuropathy, and gut microbiome disturbances, which cause dysmotility in the gastrointestinal tract [4-8]. However, data on the relationship between worsening of GI symptoms and glycemic control are lacking or controversial [9-11].

Abundant evidence has demonstrated that smoking is associated with increased risk of type 2 diabetes and cardiovascular disease among diabetic patients [12-15]. Cigarette smoking has been reported to be associated with GI impairment and its complications but data on smoking and diabetic control related GI complaints are still lacking [16-18].

We aimed to determine the most frequent GIC and a relationship between GIC, smoking and glycemic control by glycated hemoglobin (Hb1Ac%) and Fasting Plasma Glucose (FPG) in Diabetic Outpatient Patients (DOP). We also aimed to find the potential factors that may be associated with the presence and the absence of GIC in outpatient care.

Methods

The cross-sectional study was performed. All consecutive outpatient care patients were asked to participate in the study from three Vilnius outpatient clinics, Lithuania. The study protocol was approved by the local bioethics committee in all three outpatient clinics: The public institution Vilnius District Central Policlinic, The public institution Central policlinic and the public institution Seskine Policlinic. The GI complaints questionnaire was created for the study. The questionnaire was completed at the doctor's visit. All participants' consent has been obtained from each patient after full explanation of the purpose and nature of the study before entering study and answering questionnaires and they were not given any specific instructions relating to the management of diabetes. Inclusion criteria were adult outpatient patients (≥18 years of age); had no urgent health issues; were mentally capable to understand the study's protocol (patients' information and the consent form).

202 patients agreed to participate and 189 outpatient patients (58 males, 131 females; 54.5±5.8 years) were included into the study. 13 patients were rejected during the study due to incomplete or incorrectly completed questionnaires. The diagnosis of DM was obtained from the medical history records. 65 (34,4%) of patients had DM and 124 (65,6%) patients were non-diabetic (non-DM). Medical history on current smoking was collected.

The questionnaire contained detailed information about the patient's subjective assessment of GIC. The following GIC were defined such as: the existence of overall GIC (patient's subjective assessment), defecation, diarrhea and constipation frequency, abdominal bloating, weakness on daily basis, abdominal pain, loss of weight (within the last year), steatorrhea (fatty feces; subjective assessment of flushing of feces from toilet walls), stool consistency (assessed as mostly soft/normal/mostly fragmented). Symptoms were evaluated by a Likert scale. Information about consumption of Pancreatic Eenzyme Rreplacement Therapy (PERT) was taken from the patient's anamnesis. Subjects in the DM group were assessed as one - diabetic group - regardless of DM type, as there were no significant differences between the two - type 1 diabetes and type 2 diabetes subgroups. There were no patients with pancreatogenic diabetes. Information about DM diagnosis, duration, monitoring by self-assessed glucose controlling at home and treatment was registered. The most recent (but not older than of the last 4 months) results of HbA1c% and FPG data were obtained from the patient's medical records.

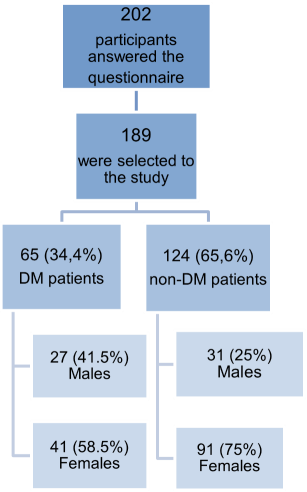

Figure 1: Patients' distribution.

Additionally, data about glycemic control based on the last documented FPG and HbA1c% were collected.

The analysis of the relationship between GIC frequency and glycemic control was performed only among diabetic patients.

For statistical analysis Chi-square ($\chi 2$) test and ANOVA test were used. Statistical analysis was performed by using IBM SPSS 21.0 and Microsoft Excel programs.

Patients' Distribution

Patients' distribution is shown in Figure 1, 202 patient's participated and 189 patients were included into the study. There were 58 males and 131 females. 65 (34,4%) of patients had DM and 124 (65,6%) patients were non-DM.

Results

Baseline Characteristics of Participants

The baseline characteristics of the study participants are shown in Table 1, 131 (69.3%) of participants were females and 58 (30.7%) were males, the mean age was 54.5 (±5.8) years.

Forty-five (23.8%) of participants were current smokers. There was no significant relationship between gender and smoking in the DM group (p=NS). Baseline characteristics of the patients are shown in Table 1.

Table 1: Socio-demographic features and body mass parameters in outpatient patients.

	Diabetic patients (N=65)	Non-diabetic patients (N=124)	p value
Males	27(41.5%)	31(25%)	.015
Females	38(58.5%)	93(75%)	
Age (mean)	59.34±13.58	50.57±18.16	.001
BMI	30.56±8.35	25.64±6.47	<.001

The Rate of Gastrointestinal Complaints, Smoking in DM and non-DM Patients Groups

The rate of GIC is shown in Table 2.The rate of pancreatic exocrine insufficiency related gastrointestinal complaints in diabetic and non-diabetic outpatient patients The most prevalent complaints of all study patients were abdominal bloating (72%), weakness on a daily basis (66,1%) and diarrhea (46%). In DM patients' group overall presence of GI complaints (49.2% vs. 41.1%, p=0.001), abnormal defecation frequency (23.1% vs. 10.5%, p=0.020), diarrhea (60% vs. 38.7%, p=0.004), weakness on a daily basis (75.4% vs. 61.3%, p=0.036), steatorrhea (58.5% vs. 26.6%, p<0.001) and altered stool consistency (40% vs. 21.8%, p=0.007) were more common in comparison with non-DM patients' group.

No statistically significant difference was found between any GIC among smokers and non-smokers outpatient care patients (p=NS).

The Relationship Between GIC Frequency and the value of FPG and Smoking in Outpatient Diabetic Patients

The significant relationship between glycemic control and GIC was found. Patients with frequent overall presence of GIC had worse glycemic control by FPG compared to those with no complaints and those whose complaints were described as "sometimes" (8.68±3.22 mmol/l vs. 6.07±1.85 mmol/l vs. 6.37±1.29 mmol/l; p<.001).

Increased defecation frequency was associated with higher FPG values in comparison with normal defecation frequency and less frequent defecation (9.10±2.66 mmol/l vs. 6.24+/-2.13 mmol/l vs. 5.76±.53 mmol/l, p<.001), but FPG value was significantly lower in patients with constipation compared to those who did not experience constipation (5.88±1.98 mmol/l vs 6.76±2.39 mmol/l, p=.017).

Subjects with persistent weakness were found to have higher fasting plasma glucose values compared to those who had never experienced weakness (7.82±2.83 mmol/l vs. 5.87±1.12 mmol/l, p=.033).

A statistically significant difference was found between altered feces groups. FPG values were significantly higher in those subjects whose feces were mostly of soft consistency, compared to those with normal feces consistency and fragmented stools (8.52±1.78 mmol / l vs. 5.97±1.78 mmol/l, p<.001 vs. 6,00±1.71, p=.001).

The FPG value was significantly higher in subjects who had steatorrhea (referred as fatty, oily feces that are difficult to flush down the toilet walls) compared to subjects who did not report such a complaint (7.82±2.69 mmol / l vs. 5.78±1.69 mmol / l; p<.001).

There was a statistically significant difference between the groups of PERT usage. The FPG value was significantly higher in subjects who used the PERT to improve gastrointestinal function compared to subjects who did not use the PERT (7.43±2.87 mmol/l vs. 5.85±1.54 mmol/l; p<.001).

In the context of diabetes control by FPG means, no significant relationship was found between the complaints of abdominal pain, abdominal bloating, and loss of weight (p=NS).

No statistically significant difference was found between any GIC frequency and the value of FPG among smokers and non-smokers outpatient care patients (p=NS).

The Relationship between GI Complaints Frequency and the Value of HbA1c%, and Smoking in Outpatient Diabetic Patients

There was a significant relationship between long-term glycemic control and GIC. HbA1c% values were significantly higher in those diabetic patients with frequent overall presence of GIC compared to those with no GIC and patients with GIC described as ''usual'' (8.56±1.79% vs. 7.26±1.36% vs. 7.64±1.95% p=.040).

The HbA1c% value was significantly higher in subjects with higher defecation frequency compared to subjects who did not complain of altered bowel movements and those who had reduced bowel movements (8.90±2.42% vs. 7.52±1.43%; p=.043 vs 6.33%.±.58%; p=.047; p=.020).

A statistically significant difference of the HbA1c% parameter value was found between all groups of abdominal bloating complaints (p=.040). (Table 3 Gastrointestinal complaints and experienced frequency of complaints in relation to glycemic control by fasting plasma glucose and glycated hemoglobin in outpatient diabetic patients).

Subjects who consistently complained on weakness were found to have a statistically higher value of the HbA1c% compared to those who had never experienced weakness (9.30±2.68% vs 6.96±0.78%, p=.017). A significant difference of the HbA1c% value was found between the groups of the weakness (p= .031). (Table 3.Gastrointestinal complaints and experienced frequency of complaints in relation to glycemic control by fasting plasma glucose and glycated hemoglobin in outpatient diabetic patients).

Those subjects who observed steatorrhea as fatty feces had higher HbA1c% values compared to those who did not complain about fatty feces. (7.97±1.41% vs. 5.87±1.85%; p<.001).

Subjects with PERT usage were found to have higher HbA1c% values compared to subjects who did not use PERT (7.01±.86% vs. 8.27±1.99%; p=.003). No significant relationship was found between the complaints of abdominal pain, loss of weight, diarrhea and constipation and HbA1c% (p=NS).

Table 2: The rate of pancreatic exocrine insufficiency related gastrointestinal complaints in diabetic and non-diabetic outpatient patients.

Complaints	Diabetic patients (N=65)	Non-diabetic patients (N=124)	p
The overall presence of GIC (subjective assessment)	40(49.2%)	51(41.4%)	**.001**
Abnormal defecation frequency (diarrhea/ constipation)	15(23.1%)	13(10.5%)	**.020**
Diarrhea	39(60%)	48 (38.7%)	**.004**
Constipation	15(23.1%)	44(35.6%)	NS
Abdominal bloating	29(44.6%)	54(43.5%)	NS
Weakness on a daily basis	49(75.4%)	76(61.3%)	**.036**
Loss of weight (within the last year)	10(15.4%)	24(19.4%)	NS
Abdominal pain	4(6.2%)	14(11.3%)	NS
Steatorrhea	38(58.5%)	33(26.6%)	**<.001**
Altered stool consistency	26(40%)	27(21.8%)	**.007**

*No statistically significant difference was found between any GI complaints among smokers and non-smokers (p=NS) outpatient patients.
GIC: Gastrointestinal Complaints

Table 3: Gastrointestinal complaints and experienced frequency of complaints in relation to glycemic control by fasting plasma glucose and glycated hemoglobin in outpatient diabetic patients.

Complaints	Frequency	FPG	HbA1c%
Overall presence of GIC	Frequent	8.68±3.22	8.56±1.79
	Sometimes	6.37±1.29	7.64±1.95
	No GIC	6.07±1.85	7.26±1.36
	p value	**<.001**	**.040**
Defecation frequency	Higher defecation frequency	9.10±2.66	8.90±2.42
	Normal defecation frequency	6.24±2.13	7.52±1.43
	Lower defecation frequency	5.76± .53	6,33± .58
	p value	**<.001**	**.020**
Constipation	Constipation	5.88±1.98	6.50± .71
	No constipation	6.76±2.39	7.77±1.61
	p value	**.017**	=NS
Diarrhea	Frequent	8.16±2.14	8.33±2.65
	Sometimes	9.39±3.22	8.55±1.64
	Rarely	6.23±2.18	7.71±1.81
	Never	5.93±1.72	7.07± .85
	p value	**<.001**	=NS
Bloating	Frequent	6,85±2,14	8.86±2.80
	Sometimes	6,99±2,82	8.12±1.74
	Rarely	6,16±2,15	7.37±1.42
	Never	6,01±1,65	6.99±0.74
	p value	=NS	**.043**
Weakness	Frequent	7.82±2.83	9.30±2.68
	Sometimes	6.60±2.26	7.69±1.38
	Rarely	6.73±2.87	7.80±1.77
	Never	5.87±1.12	6.96± .78
	p value	**.024**	**.031**
Abdominal pain	Yes	5.85±1.18	7.00± .82
	No	6.52±2.36	7.74±1.73
	p value	=NS	=NS
Loss of weight (within the last year)	Yes	6.12±1.88	7.11± .93
	No	6.55±2.38	7.79±1.77
	p value	=NS	=NS
Steatorrhea	Yes	7.82±2.69	7.97±1.41
	No	5.78±1.69	5.87±1.85
	p value	**<.001**	**<.001**
PERT usage	Yes	7.43±2.87	8.27±1.99
	No	5.85±1.54	7.01± .86
	p value	**<.001**	**.003**

PERT: Pancreatic Enzyme Replacement Therapy
FPG: Fasting Plasma Glucose; *mmol/l*
HbA1c%: Glycated Hemoglobin; *%*

No statistically significant difference was found between GI complaints frequency and the value of HbA1c%, among smokers and non-smokers outpatient care patients (p=NS).

Discussion

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control [19]. Smoking is a well-established risk factor for cardio-vascular diseases in the general population, and accumulating evidence demonstrates that smoking increases risks of macrovascular complications in diabetic patients [19,20]. Also, cigarette smoking is associated with insulin resistance [15,21]. There is a number of studies which show the association between GI symptoms and poor glycemic control in DM population and smoking [12,13]. Smoking both negatively affects pancreatic β-cell function, reducing insulin secretion, as well as inducing an inflammatory response which could lead to chronic pancreatitis [14]. However, we found no statistically significant difference between any GIC among smokers and non-smokers in outpatient patients in our study. Data suggest that glycemic control may be more significant for diabetic patient in gastrointestinal complaints rather than smoking - a well established GIC factor. However, as only a small portion of participants were smokers, our results on smoking association should be interpreted with caution.

The gastrointestinal tract can become the target of abnormalities during the development and progression of diabetes [22]. The prevalence of GIC is increased in diabetes [23], but their natural history is understood poorly [24], and any impact of glycemic control is controversial [9]. Gastrointestinal complications of diabetes are often caused by abnormal GI motility, which is a consequence of diabetic autonomic neuropathy involving the GI tract [23], however, epidemiologic data are still controversial. Another risk factor is hyperglycemia, which may precipitate dysfunction throughout the alimentary tract [24]. In recent years there are more studies on DM and GI relationship, but data on this topic and the association with glycemic control in outpatient diabetic patients are lacking [2,3]. Moreover, GIC are not always taken as a serious diabetic related issue for diabetic patients, especially in those with diabetic exocrine pancreatopathy, which is known as moderate-to-severe subclinical pancreatic fibrosis and modest exocrine dysfunction, which occurs in the absence of clinical or histopathological evidence of chronic pancreatitis in type 1 and 2 DM [25,26].

Also, there is a significant number of patients with already established exocrine pancreatic insufficiency: patients usually present to their general practitioner with non-specific symptoms. Diagnosis requires a high index of suspicion with a careful medical history and clinical examination, and early intervention for borderline patients [27]. We compared DM and non-DM outpatient patients' populations of which 49.2% percent of diabetic patients reported chronic complaints from the gastrointestinal tract of which weakness was the most common (75.4%). The study by Reszczyńska et al. found 75% of diabetic patients having chronic symptoms associated with incomplete defecation being most common [4]. We found that GIC in subjects with DM differed from nondiabetic subjects. Four GIC were found to be frequent among diabetic subjects but not among non-diabetics: diarrhea, weakness, steatorrhea and altered stool consistency. Abdominal bloating was common to both diabetics and non-diabetics, half of the population of both groups had this symptom.

The principal GIC linked to the manifestation of the DM include abdominal pain, diarrhea, nausea, flatulence, and vomiting [4,5,28]. Studies show that poorly controlled type 2 diabetes mellitus is a major international health problem [29,30]. It was found that gastrointestinal symptoms are twice as common in type 1 diabetes and associated with poorer quality of life and glycemic control [28]. Amongst the diabetic complications with the highest symptom burden, yet frequently under recognized and not treated is diabetic enteropathy. Hyperglycemia significantly alters the microenvironment within the diabetic enteropathy [5]. Part of the cross-sectional epidemiological studies have suggested that GI symptoms are associated with poor glycemic control [2]. We also observed that poor glycemic control measured by FPG or by HbA1c%, was associated with some GIC. There was a relationship between GIC and poor glycemic

control by FPG. Higher defecation frequency, constipation, diarrhea, and weakness were significantly more often seen as complaints in the poor glycemic control group when evaluated by FPG. Other studies suggested that there was no clear association between GI symptoms and change in acute glycemic control [9].

We also found a relationship between the poor long-term glycemic control measured by HbA1c% and GI complaints. Higher defecation frequency, bloating, steatorrhea, and weakness were significantly more common as the measured HbA1c% was higher. In a cross-sectional questionnaire study of 1101 diabetic subjects (with part of participants recruited from outpatient clinics) by Bytzer and colleagues, the subset of patients who had HbA1c measured, poor glycemic control was associated with upper GI symptoms (dysmotility like and ulcer like dyspepsia) [2]. As our study was driven by a small number of participants, the results should be interpreted with caution. Kim J.H. and colleagues focused on the association between upper GI symptoms and HbA1c levels. They found 3.38 times as many upper GI symptoms in the cases with HbA1c ≥8% compared to those with HbA1c <6%; all individual upper GI symptoms were common in the cases with HbA1c ≥8% [27]. Our results were similar, and we found that overall presence of GIC were described as frequent in patients who had poor glycemic control by both- FPG and HbA1c% - the evaluation of the severity and frequency of GIC can be considered as the strength of our study, as well as two objective parameters of glucose control – FPG and HbA1c%.

Weakness or fatigue is a common symptom related to EPI and is often associated with diabetes, its complications and comorbidities [25], including anemia [31], hypothyroidism [32], as well as medications usage [33]. Often neglected are psychological factors, such as depression or feeling overwhelmed by their diagnosis or complexity of medical care that can contribute greatly to feeling "low energy". In our study we found weakness being one of the most common symptoms in both –DM (75.4%) and non-DM (61.3%) patients' groups. In DM group, frequent weakness complaint was strongly associated with poor glycemic control measured both by FPG (7.82±2.83 mmol/l) and especially HbA1c% (9.30±2.68 %) as the highest value of HgbA1c% of all GIC was within frequent weakness.

The influence of diabetes on pancreatic exocrine function is not yet entirely clear. Exocrine pancreatic insufficiency, an important cause of maldigestion and malnutrition, results from primary pancreatic disease or is secondary to impaired exocrine pancreatic function and significantly affects diabetes outcomes [34]. Pancreatic insufficiency can lead to multiple clinical manifestations causing poor quality of life and potentially serious complications [35]. Clinical features of EPI are usually non-specific. These include steatorrhea, abdominal discomfort, bloating, and weight loss. Additionally, malnutrition, trace element and vitamin deficiency, metabolic bone disease (osteoporosis or osteomalacia), muscle spasms, decreased immune competence, and an increased risk of cardiovascular events frequently occur [36]. Steatorrhea is the most frequent sign of EPI; it is recognized when the fat content of stool is more than 7g/day and given that diet includes 100 g of fat a day. Fat malabsorption requires at least a 5% to 10% fall in pancreatic lipase and trypsin level [37]. Furthermore, studies on PERT usage in the DM population are lacking, even though the combination of steatorrhea and insufficient dietary intake puts patients at significant risk for malnutrition [38]. Pancreatic exocrine insufficiency has been reported to be common in diabetics, with a prevalence widely ranging, in different studies [25,39]. In populations with type 2 DM autonomic neuropathy and microvascular damage may play a key role in inducing pancreatic atrophy and fibrosis [4]. As there are no clear guidelines for the use of PERT in the DM treatment, it is often purchased over the counter as an aid in relieving the symptoms that usually result from diabetic enteropathy. In our study, poor glycemic control measured by both FPG and HbA1c% was significantly associated with PERT usage. Future studies evaluating the influence of PERT on glycemic control should enroll a larger and more homogeneous population of diabetic patients.

The limitations of this study include the following: there was no data collected on coexisting comorbidities such as autonomic neuropathy, EPI, other gastrointestinal tract disorders; psychiatric disorders associated with GI symptoms in patients with diabetes as this might be an important factor as well as drug usage possible side effects [40]. Also, we did not evaluate the usage of drugs as possible effect towards GIC. Nevertheless, the present study is the first of its kind performed in Lithuania, in outpatient practice.

Conclusions

Gastrointestinal complaints corresponding to EPI are common in all outpatient patients, but are significantly more frequent in diabetic patients, especially with poor diabetes control, who have also been more likely to use pancreatic enzyme therapy. However, we found no significant correlation between GIC and smoking, neither in DM and non-DM outpatient patients' population – more studies are needed to confirm this finding.

Author Statements

Declaration of Interest and Funding

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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